In the detailed description, page 13, line 24-25; page 14, lines 8, 14 ; the list of biodegradable polymers now includes polypeptides and polysaccharides.

In the detailed description, page 15, lines 2-7, the list of therapeutic agents is expanded beyond chemo-embolic agents.

Example 5 has been added.

The abstract has been shortened.

Prior claims 1 and 15 (new claims 1 and 13) are amended to incorporate the subject matter of prior claims 2 and 4, and prior claims 17 and 19 respectively, and the claims re-numbered. Claims 1 and 13 are further amended to exclude low molecular weights as stated in the specification on page 8, lines 5-11.

New claims 2 and 14 recite the molar ratios added on page 10 and in the added Example 5.

New claims 32 and 38 recite biodegradable polymers now including polypeptides and polysaccharides.

New claims 12 and 30 recite specific therapeutic agents as in the description on page 15, lines 2-7.

REMARKS

The Examiner stated that the abstract is longer than 25 lines. Applicant believes that the above amendment brings the abstract within 25 lines.

Restriction

Applicant regrets the confusion caused by the original claim language. Please note that claim 1 now recites exclusion of low molecular weight species. Referring now to the Examiner's position that the composition of Group I can be made in a manner wherein no low molecular weight polymer is produced such as living polymerizations, Applicant says that living polymerization is known in the art as an efficient method to obtain homopolymers or block copolymers with exceedingly narrow molecular weight distribution. However, it is also known in the art that the living polymerization is not

suitable for obtaining random copolymers involving comonomers of different reactivities. Living polymerization is an ionic polymerization and requires use of ionic initiators. Ionic polymerization is not suitable for obtaining random copolymers of comonomers of different reactivities as is the case of N-akyl substituted (meth-)acrylamide and a hydrophyllic co-monomer, for example N-isopropylacrylamide and acrylic acid. The applicant will supply a reference if the Examiner deems it necessary. Accordingly, the Examiner's suggested method is inoperative and therefore unsupportive of the Restriction requirement.

The Examiner's next observation is that Applicant claims adding a therapeutic agent to the copolymer and that one could make the composition by copolymerizing the therapeutic agent to the copolymer. Applicant has not found a way to do that and preserve the gelling properties of the final product. Adding a therapeutic agent with the [meth-]acrylamide and the hydrophylic comonomer is believed to interfere with the gelation temperature of the final composition so that the final composition would not gel. Again, Applicant believes the Examiner's suggested method to be inoperative and therefore unsupportive of the restriction requirement. It is respectfully requested that the finality of the restriction requirement for Groups I and II be withdrawn and these two groups rejoined in the present application.

Applicant accedes to the restriction of Group III (claims 31-46).

35 USC 112

The Examiner says that the phrase "chemo-embolic" is not art recognized. However, Applicant would like the Examiner to consider the titles of the following articles:

1. S. Kobayashi et al.: Trancathether hepatic arterial chemo-embolization using epirubicin-lipiodol, Cancer Chemother. Pharmacol. (1992), 31, Suppl.I, S45-S50, and

2. J.C. Trinchet, M. Beaugrand: Hepatocellular carcinoma: treatment with arterial chemo-embolization, Presse Med. (PMT), 23(18), 831-833, 1994, (underlining added).

Because these articles are 4 and 6 years past, Applicant believes that the "chemo-embolization" is now well known in the art and a grammatical variant of "chemo-embolic" would be understood as such.

35 USC 102 and 103

Upon studying Bae et al., Applicant notes that Bae et al. column 10, lines 41-50, says:

> This suspension will be injected . . . and the polymer **14** will collapse . . . as the temperature is raised to or above the LCST. Decreasing the temperature . . . will solubilize the collapsed matrix . . .

The reason that the polymer or matrix collapses is the result of expulsion of water or "synerisis" upon gelation. Note that Applicant specifically avoids substantial synerisis by controlling the amount of hydrophyllic comonomer to be less than about 10 mole% as recited in Applicant's claim 1 and explained in Applicant's Specification page 9, lines 8-16, and page 13, lines 9-15. Synerisis is defined on page 9, lines 15-23 of Applicant's specification. Thus, Applicant believes that the Bae lacks recitation of achieving gelation with substantially no synerisis.

Upon inspection of Sassi et al., Applicant notes column 5, line 64 through column 6, line 1 which says:

> . . . below the Tm the hydrogel is present as a gel like composition . . . Above the Tm of the hydrogel, the hydrogel is present as a flowable, pourable composition . . .

This is exactly opposite of Applicant's gelation upon heating from a lower temperature where the mixture is a flowable liquid solution. Applicant attributes this difference in function to a difference in material composition set forth in claim 1 reciting N-alkyl substituted [meth-]acrylamide. Applicant believes that this subject matter is not found in Sassi et al.

Closure

Applicant has made an earnest attempt to place the above referenced application in condition for allowance and action toward that end is respectfully requested. Should the Examiner have any further concerns, he is invited to contact the undersigned by telephone.

Respectfully Submitted,

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THE UNDERSIGNED HEREBY CERTIFIES THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231, ON THE DATE SET FORTH BELOW.

Janice Taylor 1/15/99
DATE